BH4 deficiency with unusual presentations: Challenges and lessons

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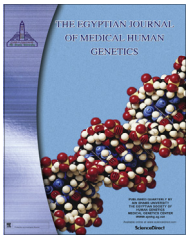

EDITORIAL

BH4 deficiency with unusual presentations: Challenges and lessons

Dear Editor,

We have recently encountered with a 9 month old boy, the second in birth order of non-consanguineous parents who presented to the genetics clinic by coma. He was born by cesarean section due to decreased fetal kicks with a birth weight of 2.8 kg. The main complaint of the parents before his presentation was the severe failure to thrive documented by his weight of five kg at presentation. He had global developmental delay as he was unable to support his head till the age of 6 months and was unable to sit till his presentation. He was able to reach objects at the age of 6 months but was not able to transfer objects from one hand to the other. He was able to recognize his parents at the age of 6 months.

At the age of 8 months, he had an event of pneumonia and a week later he developed convulsions that progressed rapidly to coma and was diagnosed as encephalitis. He received anticonvulsants, antibiotics, antiviral treatments with no response regarding coma recovery although his chest infection improved and the convulsions were controlled. Brain magnetic resonance Imaging (MRI) brain revealed bilateral deep cerebral white matter hypomyelination. Both metachromatic leukodystrophy and Krabbe disease were excluded by enzyme assay. The patient was then referred to exclude metabolic encephalopathy. Extended metabolic screen was done by tandem mass spectrometry and showed increased phenylalanine level to 748 μmol/l (normal 0–180) and increased glycine level of 657 (normal 0–341). Urinary organic acids showed increased phenyl lactic, phenyl acetic and phenyl pyruvic acid. Urine neopterin and biopterin analysis showed low biopterin (0.14 mmol/mol creatinine, normal value = 0.70–5.300) and elevated neopterin (60.66 mmol/mol creatinine, N = 1.20–14.50) indicative for tetrahydrobiopterin (BH4) biosynthesis deficiency, specifically 6-pyruvoyltetrahydropterin synthase (PTPS) deficiency which was confirmed by molecular testing which revealed homozygous for c.200C > T, p.(Thr67Met) of the 6-pyruvoyltetrahydropterin synthase (PTS) gene. Unfortunately the patient died before testing result of the urine neopterin was finished.

Discussion

BH4 deficiency is considered a very rare disease with an estimated prevalence of one in million live births in western countries and expected to be higher in some Mediterranean countries [1]. Actually, it is a group of diseases with several enzymes involved including GTP cyclohydrolase 1, sepiapterin reductase, 6-pyruvoyl-tetrahydropterin synthase, pterin-4-alpha reductase and dihysropteridine reductase [2]. The clinical presentation is more severe than phenylalanine hydroxylase deficiency because it involves CNS neurotransmitters biosynthesis, most commonly progressive mental retardation that is unresponsive to treatment with low phenylalanine diet, abnormal movement, impaired tone and convulsions [3].

As far as our knowledge, coma was not reported before in patients with BH4 deficiency. The diagnosis of this patient was a challenge for the treating physician, not only due to the atypical presentation but also because of the MRI brain finding of severe hypomyelination. The presence of white matter affection in patients with untreated PKU should not misdirect the physician and restrict his diagnosis only to lysosomal storage diseases. The high phenylalanine level competes with other large neutral amino acids (LNAA) for a carrier responsible for their uptake into the CNS. The low level of LNAA may inhibit the development of myelin. These abnormalities tend to be more frequent and more severe in older patients who are off treatment and those with higher phenylalanine levels [4].

Why this patient was not diagnosed before his presentation will be the second lesson to the young physicians. The patient had two important signs that should have directed the physician to exclude inborn errors of metabolism: global developmental delay and failure to thrive. Although newborn screening for phenylketonuria (PKU) is now available in Egypt, it was not established except few months ago and still do not cover all governorates and so the diagnosis of PKU should be excluded in every child with global developmental delay.

Whether the earlier diagnosis would have saved this patient or not will still be an argument. Only few studies have reported the long-term outcome of patients with PTPS deficiency.

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The overall developmental delay after treatment was 38% (35% in those with early diagnosis and 44% of those with late diagnosis). The study was done on only 26 patients [5]. In another study the outcome of the severe form of PTPS deficiency was influenced by the precocity of the treatment [6].

The third lesson is that taking samples in critically ill patient is of high priority for proper genetic counseling to the family. Without this step, this patient would have never been diagnosed and the family would have been counseled that the child had a severe form of infection that passed to his CNS and have led to his death.

To conclude, BH4 deficiency can present an encephalopathy like picture. Reaching an accurate diagnosis is crucial not only because of the importance of initiation of early treatment but also for proper genetic counseling and family planning.

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